

Seventh Quarterly Progress Report  
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**The Neurophysiological Effects of  
Simulated Auditory Prosthesis  
Stimulation**

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## 1 Introduction

The purpose of this contract is to investigate issues involving the transfer of information from implantable auditory prostheses to the central nervous system of individuals using these devices. This investigation is being pursued along multiple parallel tracks and include the use of animal experiments and computer model simulations to:

- Characterize fundamental spatial and temporal properties of intra-cochlear stimulation of the mammalian auditory nerve.
- Evaluate the use of novel stimuli and electrode arrays.
- Evaluate proposed enhancements in animals with a partially degenerated auditory nerve.

In this seventh Quarterly Progress Report, we focus on work recording the EAP in both guinea pigs and cats in response to constant amplitude trains of pulses. The patterns of response to these stimuli can be affected by a number of factors including refractory effects and stochastic patterns of the underlying neural responses. The effects of several stimulus parameters are described in the first part of this report. Some initial model results which can simulate effects of stimulus level are also described. The second part of the study described in this report evaluates the use of two stimulus conditioners which can have an effect on the response patterns to trains of pulses.

This work comprises part of the dissertation submitted by Akihiro Matsuoka as part of the requirements for Ph.D. degree in Speech and Hearing Science from the University of Iowa.

## 2 Summary of activities in the seventh quarter

- Collected single-fiber and gross potential responses from three cat preparations. Completed data analysis for two of these three cats. Collected EAP data from one guinea pig.
- Two presentations of work done under this contract were presented at the Seventh Symposium on Cochlear Implants in Children, Iowa City, IA. (see Appendix A for abstract).
- One presentation of work done under the contract was presented at the Fourth European Symposium on Pediatric Cochlear Implantation in s'-Hertogenbosch, The Netherlands (see Appendix A for abstract).

- Completed preparation of a manuscript focusing on the basic response properties of cat auditory nerve fibers to monophasic, monopolar electrical stimulation. (Some of this material was presented in the last progress report). This manuscript will be submitted along with a companion paper, described below.
- Began work on another manuscript that will relate the patterns of experimentally recorded single-fiber responses to the gross, whole-nerve action potential of cats.

### **3 Compound action potentials evoked by electrical pulse trains: Effects of stimulus parameters on response pattern**

#### **3.1 The goal of the study**

In processors using continuous interleave sampling (CIS), the amplitude of the stimulus pulses encodes information about amplitude of the input (speech) waveform. One can then assume that if the stimulus amplitude (across the train of pulses) is constant, it would be desirable for the auditory nerve to respond with constant-amplitude responses. However, experimental results from humans and animals show that electrically evoked compound action potentials (EAP) to trains of constant-amplitude pulses can demonstrate a distorted response pattern, often with an alternating pattern of response amplitude. These non-uniform EAP responses are presumably due to the combined effects of highly synchronized responses to electrical stimulation and refractory effects (Wilson et al., 1994).

Given the above considerations, a greater understanding of EAP responses to constant-amplitude pulse train stimulation could be important in developing new strategies for better signal representation with processors using CIS (or amplitude-modulated pulse train) encoding strategies. In this study, we first characterized the response to pulse trains while varying stimulus waveform (pseudomonophasic vs biphasic), stimulus polarity, stimulus level, and interpulse interval. The pattern of response amplitude was measured to evaluate the degree of alternation and refractory properties induced under these different stimulus conditions. In the second part of this study, we investigated the response to novel, alternative stimulus configurations that employed either wide-band noise or high-rate, low-level pulses as background conditioners. The extent to which these conditioner stimuli could

reduce the level of across-fiber synchrony and hence, the level of the amplitude alternation (i.e., distortion) in response to constant-amplitude pulse train stimulation, was evaluated. In the case of the wide-band noise conditioner, it is likely that this "noise" imposed across fibers is correlated, but the signal averaging technique used here results in independent noise samples averaged across time. The use of signal averaging across stimulus presentations, each presentation with an independent noise sample, is analogous to the summation of responses from different channels where each channels is stimulated by an independent noise source. The possibility of enhanced stimulus encoding by means of across-fiber desynchronization with high-rate pulse trains was discussed in QPR 5 and in Rubinstein et al. (submitted). High-rate pulses are evaluated here in their ability to reduce response alternation to interleaved low-rate pulses.

### **3.2 Methods**

Thirteen adult cats (4-5 kg) and eighteen guinea pigs (400-600g) were used as subjects in acute preparations. Complete data sets were collected from three cats and three guinea pigs. More limited data were collected from ten cats and fifteen guinea pigs. In both preparations, the auditory nerve was exposed to facilitated direct-nerve EAP recordings. The cochleae were acutely deafened with infusion of Neomycin sulfate. As in our previous measures of the EAP, a monopolar stimulating electrode was placed in the basal turn of the scala tympani through the round window. The methodology has been described in detail in QPR 1 and Miller et al. (1998).

Both pseudomonophasic and biphasic pulse train stimulation were used. The former provides the more place-specific excitation possible with monophasic stimulation, while the latter affords comparisons with the stimulus modality typically used in clinical devices. The pseudomonophasic pulses consisted of a short-duration pulse followed (without delay) by a long-duration phase of opposite polarity but equal charge (typically 40  $\mu$ s phase followed by a restorative phase of at least 160  $\mu$ s). The biphasic pulses also had charge-balanced waveforms, but with equal amplitude and duration of each opposing phase. These waveforms are shown schematically in Figure 1. Durations of pulse trains were typically 100 ms. The interpulse intervals (IPI) within the train varied from 0.6 ms to 16 ms. In the experiments using additive noise paradigm, the pseudomonophasic pulse train was mixed with a continuous wide-band noise (20 kHz upper cutoff frequency) noise and applied to the stimulating electrode. The scheme of this stimulus condition is shown

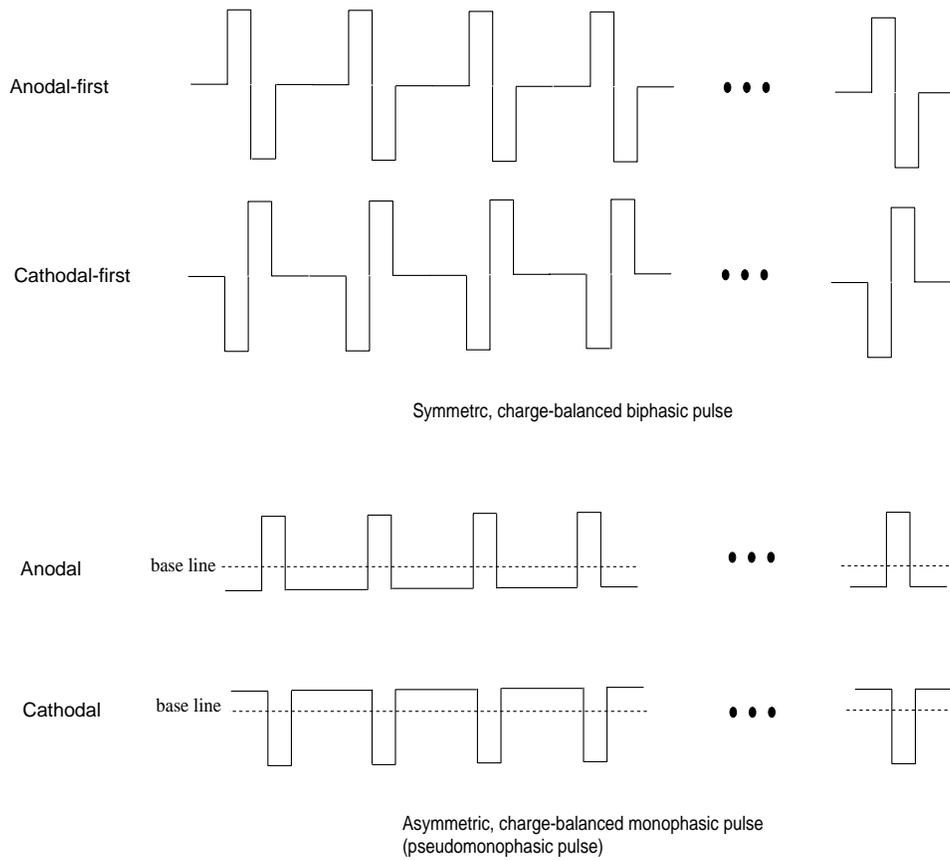


Figure 1: Two stimulus waveforms used in this study.

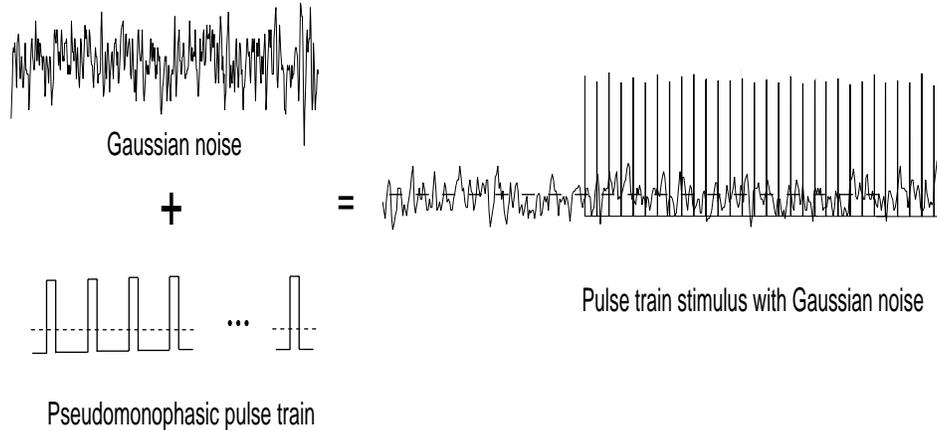


Figure 2: The stimulus paradigm for noise conditioner experiments. Onset of noise was at least 50 ms before the first pulse was presented.

in Figure 2.

The stimulus paradigm for high-rate pulse train stimulation is shown in Figure 3. High-rate pulses (IPI=0.2 ms) were presented for 50 ms prior to the onset of a low-rate pulse. Then, the low-rate stimulus (usually at a 1 kHz rate, was delivered for 80 ms. Since the high-rate pulse train with IPI of 200  $\mu$ s may elicit the EAP response which can overlap those in response to the interleaved low-rate EAP response, a subtraction method was used to examine each EAP response sequence. With this technique, the EAP responses up to  $n_{th}$  pulse and  $(n - 1)_{th}$  were both measured. The  $(n - 1)_{th}$  response was then subtracted from  $n_{th}$  response so an  $n_{th}$  response, devoid of influences from the  $(n - 1)_{th}$  pulses, was obtained.

EAP responses were first amplified (20 dB) and then filtered by a 6-pole Butterworth low-pass filter with a cutoff frequency of 30 kHz. Responses were digitized with 16-bit resolution and sampled at a rate of 100,000 samples/s. The number of sweeps was usually 100 to 300 depending upon the stimulus intensity and signal/noise ratio. EAP waveforms were recorded and transferred to a UNIX workstation for later analysis. As in our previ-

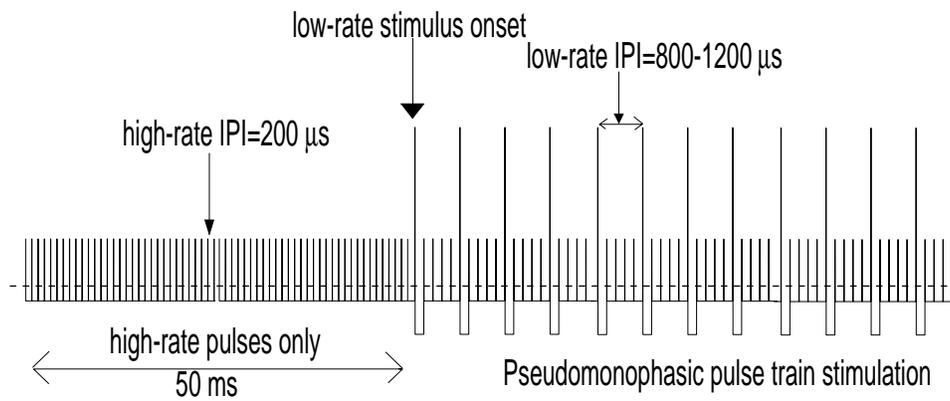


Figure 3: The stimulus paradigm of low-rate pulse train with superimposed high-rate pulse train. In order to have an effect on the response to the first pulse, high-rate pulses were presented for a duration of 50 ms before the initiation of the low-rate pulse train.

ous work, amplitude of the EAP in response to each pulse in the trains was calculated from the first negative peak (N1) to the following positive peak (P2).

Growth of the EAP response amplitude as a function of stimulus level can be approximated by an integrated Gaussian function. To reduce across-animal variability due to difference in their sensitivity to stimuli, we make comparisons among subjects at stimulus levels set at approximately 30%, 50%, 100% of the EAP dynamic range, where 100% refers to the level at which EAP amplitude is maximum. We refer to these levels as low level, middle level, and high level in subsequent figures.

### 3.3 Effects of stimulus level

Figure 4 illustrates the effect of changing stimulus level in a cat. In each graph, the response amplitude to each pulse in the train is normalized to that of the response amplitude to the first pulse. The normalized amplitudes are then plotted as a function of time after stimulus onset of the first pulse. The EAP response amplitude to the first pulse is always the greatest. Minimum EAP responses can be seen in the response to the second pulse, in response to the third, or in some cases, in response to a later pulse. Each sequence of responses displays evidence of a refractory effect in which there is a large diminution of response amplitude after that of the initial pulse. In addition, the data for cathodic stimuli show an alternating pattern of EAP response amplitude in which responses to consecutive pulses in the train alternate between high and low values. That alternating pattern is highly amplitude dependent. For the cat data shown in Figure 4, maximum EAP alternation in the cathodal response is observed at the stimulus level of 1.23 mA. Further increment of stimulus level causes a decrement of the amplitude of alternation.

In this particular example (subject and IPI), there is relatively little alternating pattern in anodal responses regardless of stimulus level. While there are clear differences with stimulus polarity as shown here, anodal stimuli can show significant alternation of the response at appropriate IPIs (see later sections).

Figure 5 shows examples from three cats for which we collected data over a range of stimulus level covering the entire dynamic range of the EAP. In order to quantify the degree of response alternation, an alternation amplitude was calculated by averaging three consecutive EAP amplitude differences in a analysis time window beginning 10 ms after the onset of the pulse train.

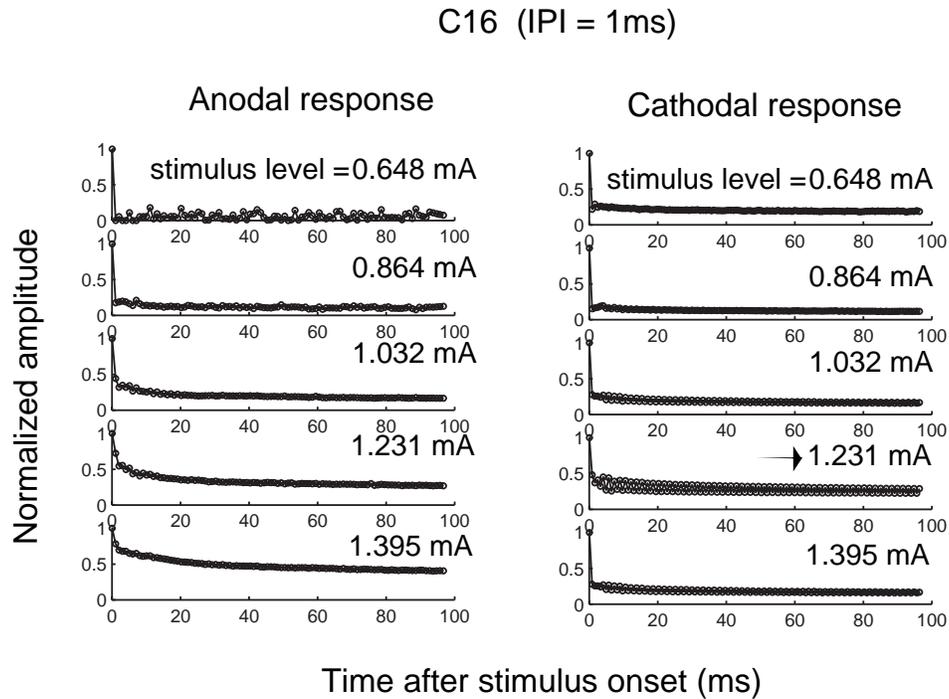


Figure 4: Normalized EAP response amplitude as a function of time after stimulus onset at five different stimulus levels. Pseudomonophasic pulse train stimulation was used in all cases. Responses to anodal and cathodal stimuli are plotted in the left and right columns, respectively. Normalization was accomplished by dividing the response amplitude to each pulse in the train by the response to the first pulse. The arrow indicates the stimulus level at which a maximum alternating pattern of EAP response is observed for cathodal stimuli.

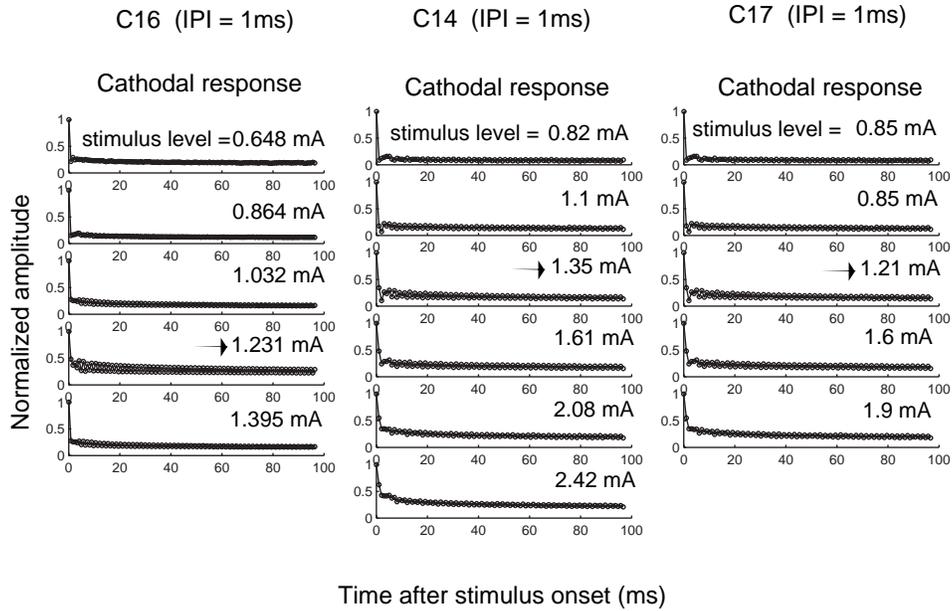


Figure 5: Normalized EAP amplitude in response to pseudomonophasic pulse trains at different stimulus levels from three different cats. The stimulus levels shown here covered the entire range of the EAP amplitude-level function. Arrows indicate the stimulus level at which the maximum response alternation amplitude was seen. The stimulus levels that elicited saturated EAP response amplitudes were 1.3 mA for C16, 1.51 mA for C14, and 1.52 mA for C17.

The maximum value calculated across the duration of the pulse train is referred to maximum response alternation. The degree of response alternation across stimulus level varied across cats. Arrows indicate the stimulus level at which the maximum response alternation amplitude occurred. In all three cats, maximum alternation occurs slightly below the stimulus level at which the growth function saturates. At levels above that, alternation is decreased in all three cats.

Figure 6 plots the maximum alternation amplitude as a function of stimulus level for 11 cats from which data were collected in this study. These data were all based on measures obtained with cathodal stimulation. As the stimulus level is increased, the alternation is also increased. With a low stimulus level, the average of alternation is 0.026, which indicates a very

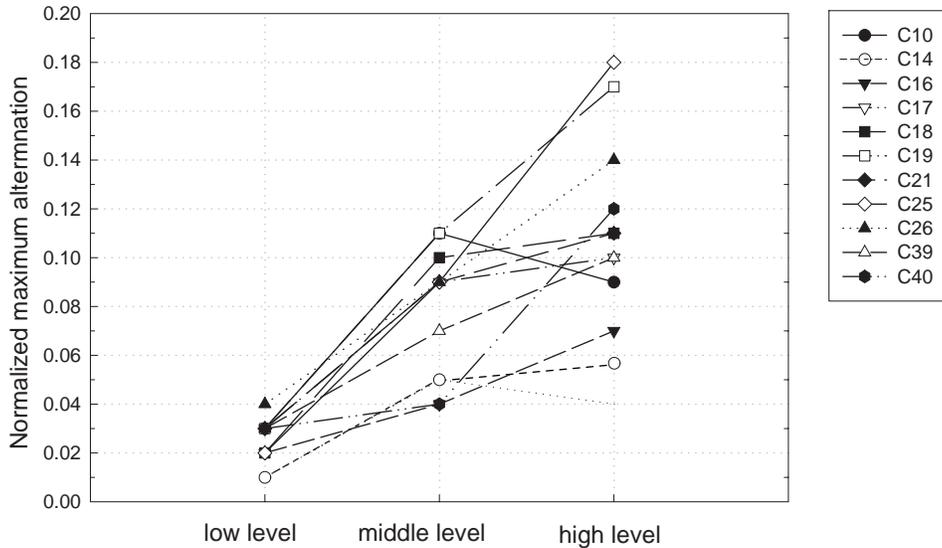


Figure 6: Normalized maximum alternation amplitude for three stimulus levels from all cats from which the data were collected. Maximum alternation amplitude for each cat was obtained from cathodal EAP response. For C10, C14, C16, C17, C18, IPI was 1 ms only. For others, IPI was varied from 0.6 ms to 8 ms. Pseudomonophasic pulse train stimulation was used except for C10, C14, C16, and C17 (these are responses with biphasic pulse train stimulation). The mean values for maximum EAP alternation for low level, middle level, and high level is 0.026, 0.08, and 0.112, respectively.

small alternation amplitude. At middle levels, the average is 0.08; at high levels, the average is 0.112.

Maximum response alternation amplitude for 15 guinea pigs are plotted as a function of stimulus level in Figure 7. As with the cat data, as stimulus level is increased, alternation generally increased (Two exceptions occur for G56 and G60). In guinea pig preparations from which more extensive measures (i.e., finer level resolution) were made, maximum alternation was typically observed near EAP saturation level. In addition, note that the degree of alternation corresponding to each stimulus level in guinea pigs is typically greater than that observed in the cat (compare Figure 7 to Figure 6).

There was a high degree of variability in the degree of alternation across animals as well as across species as shown in figures 6 and 7. In addition

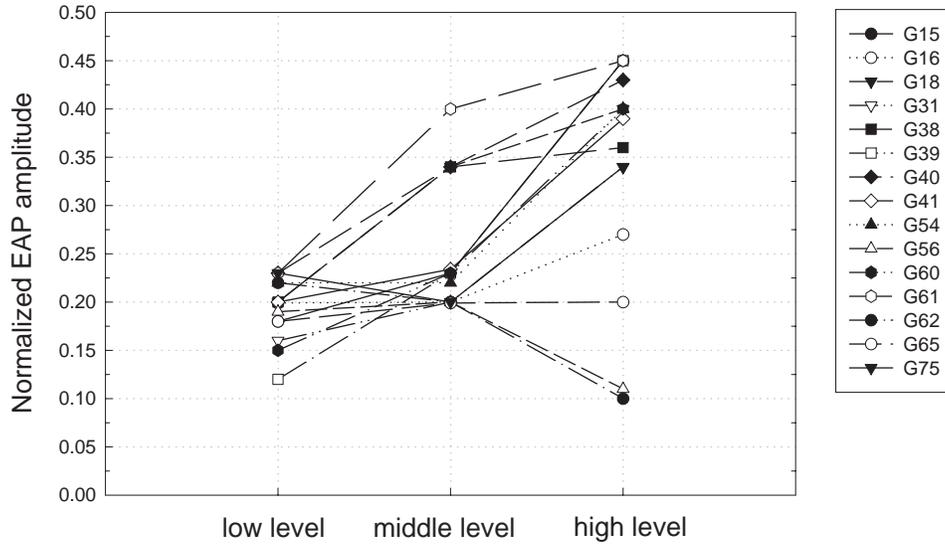


Figure 7: Normalized maximum alternation amplitude for three stimulus levels from all guinea pigs. Maximum alternation amplitude for each guinea pig was obtained from cathodal EAP response for pseudomonophasic pulse trains and from cathodal–first EAP response for biphasic pulse trains. For G15, G16, G18, and G31, IPI was 1 ms. For others, IPI was systematically varied between 0.6 and 8 ms; maximum alternation typically occurred for IPI’s between 0.6 and 2 ms. Maximum alternation was reported as the maximum occurring across all stimulus conditions. Stimuli were biphasic pulse trains for G15, G16, G18, G31, G38, G39, and G40 and pseudomonophasic pulse trains for all others.

there were several animals where we noted little, if any, alternation at any level. We have not identified specific anatomic or procedural correlates of this variability. If, however, the degree of alternation is related to stochastic nature of the underlying neural responses, then a better understanding of the contributing factors to this response could be important to pursue.

The dependence of alternation amplitude on stimulus amplitude were also simulated using the stochastic axonal model described previously (Rubinstein, 1995). The model results can be useful since they can provide possible mechanisms for some of the observed experimental effects. Figure 8 shows simulated EAP responses in the left column and EAP amplitude measurements to each pulse in the train in the right column. In each case

the EAP responses were calculated from 100 independent fibers with identical threshold characteristics. The current level of the stimulus pulse and the response of the underlying neurons (Firing efficiency or FE) is shown at the right of each graph. As the stimulus level increases, the alternation also increases. The amplitude of alternation reaches a peak at approximately 92  $\mu\text{A}$  and then decreases at higher stimulus levels. This phenomenon is consistent with the data from cat (see Figure 5) in that the degree of alternation is a nonmonotonic function of level and reaches a peak at levels where the modeled fibers underlying the EAP response reach saturation.

### 3.4 Recovery characteristics

Figures 9 and 10 show typical sequences of normalized EAP amplitudes in response to each pulse of anodal and cathodal pseudomonophasic trains. In these cases, the stimulus level was fixed at a medium level. Each graph shows response patterns for a different IPI. The minimum IPI used in each series was chosen to be long enough such that each EAP waveform did not overlap with the subsequent stimulus artifact, allowing for a straightforward measurement of response amplitude. Note that the degree of alternation in EAP response amplitude varies with both IPI and with stimulus phase. For anodic stimuli, there is relatively little alternation, with the maximum occurring at IPIs of about 1 ms or less. For cathodic stimuli, the maximum alternation is seen at longer IPIs, on the order of 2 to 4 ms.

In addition, there is an overall decrease in amplitude over the course of the responses to the 100 ms pulse train. This decrement is clearly evident in the anodal responses, but less so in the cathodal responses. For cathodal stimuli, response to the second or the third pulse decreases to a minimum and stays at approximately that level throughout the time course of the pulse train. The slow, overall, decrement seen in anodal response may be due to cumulative refractory effects or adaptation in the auditory nerve.

In this section of the study, we examined the refractory and adaptation effects evident in the cat EAP to constant-amplitude pulse trains with systematic manipulations of stimulus polarity, waveform, level, and IPI. Refractory effects were investigated by analyzing the normalized responses to the second pulse (i.e., ratio of the EAP amplitudes to the second and first pulses). Since we observed cases where the EAP to the third stimulus yielded a smaller amplitude than that to the second pulse, we also analyzed the normalized responses to the third pulse in the train. To characterize the cumulative (adaptive) effects observed across the duration of the pulse

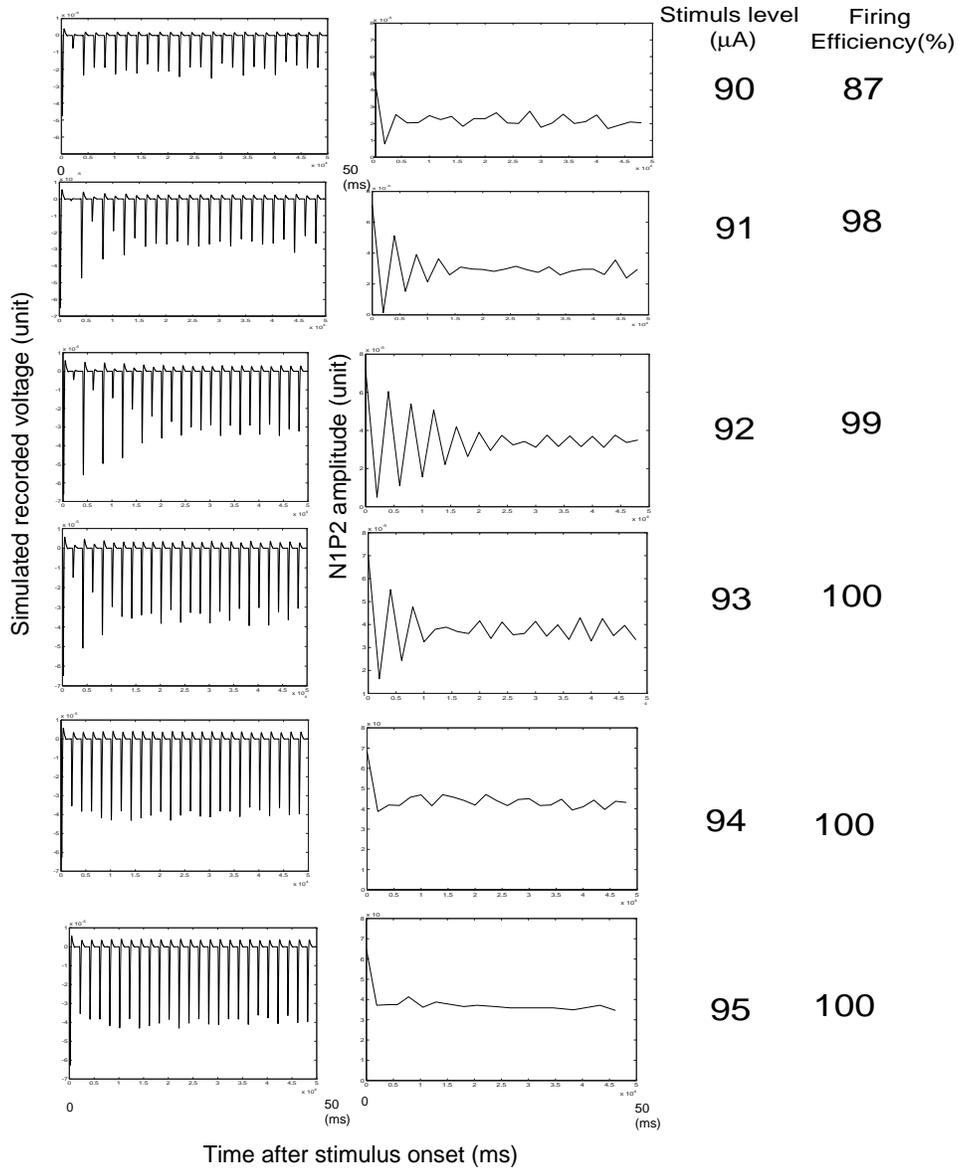


Figure 8: Simulated EAP response waveforms (left column) and EAP response amplitudes as a function of time after stimulus onset (right column) calculated by stochastic axonal model (IPI=2 ms). The stimulus level and firing efficiency of model neurons in response to the first pulse are listed at the right.

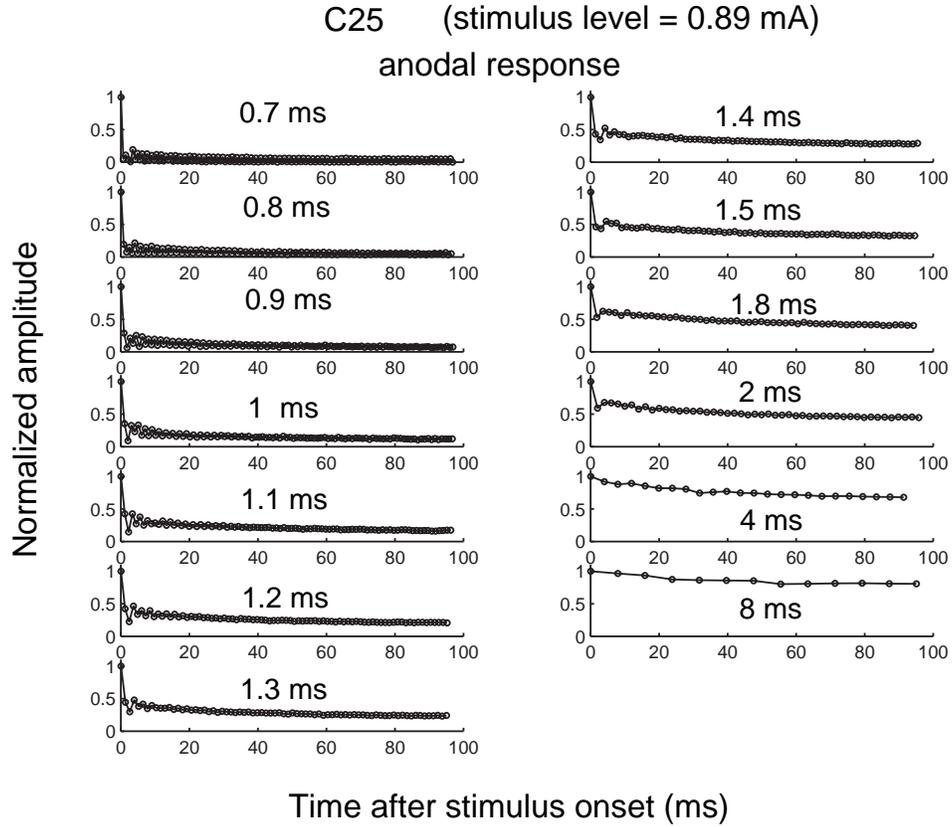


Figure 9: Normalized EAP response amplitudes for anodal stimuli as a function of time after stimulus onset for pseudomonophasic pulse trains. IPI was varied from 0.7 ms to 8 ms and is indicated in each plot. EAP response amplitudes were normalized by dividing each response amplitude by the amplitude of the response to the first pulse. The stimulus level used was 0.89 mA.

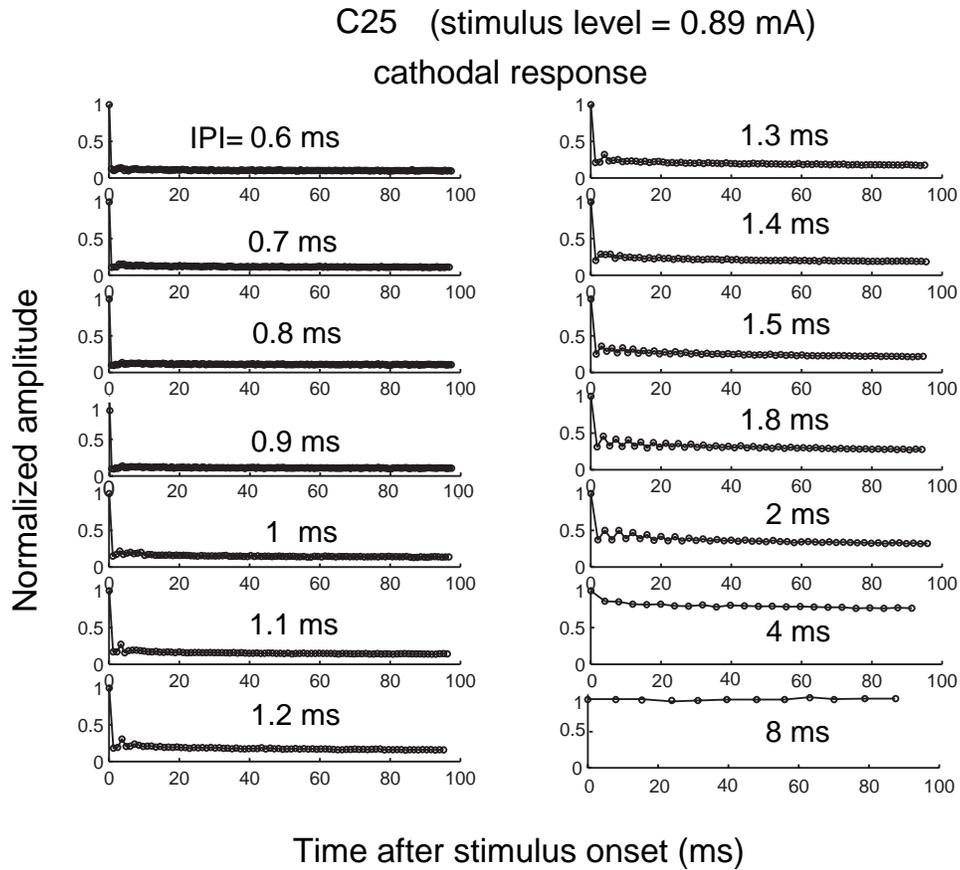


Figure 10: Normalized EAP response amplitudes for cathodal stimuli as a function of time after stimulus onset for pseudomonophasic pulse trains. IPI was varied from 0.7 ms to 8 ms and is indicated in each plot. As in the previous figure, EAP response amplitudes were normalized to the amplitude of the response to the first pulse. The stimulus level used was 0.89 mA.

trains, we also measured a "steady state" EAP response. This response was defined as the average response amplitude to all the pulses occurring 50 ms after onset of the pulse train. Like the other two measures, the steady-state amplitude was normalized to the amplitude of the response to the first pulse.

Normalized EAP amplitudes produced by second pulse with pseudomonophasic pulse train stimulation are plotted in Figure 11. Included in this figure are data from three cats (C19, C25, and C26) from which we collected data over a wide range of stimulus conditions. For each cat, stimulus levels are expressed relative to the cat's EAP threshold to facilitate across-subject comparisons. Note that full recovery of the second EAP response amplitude (i.e. normalized amplitude = 1) occurred at an IPI of 8 ms in all three cats. At shorter IPIs, the recoveries of the second EAP response amplitude were incomplete. Note that recovery at high stimulus levels was faster (i.e., closer to 1) than that produced by middle stimulus levels in C25 and C26. At both stimulus levels, anodal recovery was faster than cathodal recovery. Similar level-effects were observed with biphasic stimulation. In two of the three cases, biphasic pulse trains showed faster recovery for cathodal-first pulses than for the opposite polarity.

Normalized steady-state amplitudes are plotted in Figure 12 as a function of IPI for pseudomonophasic stimulation. Note that at an IPI of 8 ms, the steady state amplitude is close to one, indicating little cumulative refractory effect, or nearly full recovery of the EAP. At shorter IPIs, the normalized steady-state response is lower, indicating an overall decrease in the response amplitude over the course of the pulse train. Compared to the responses obtained at medium stimulus level, normalized amplitudes at high stimulus levels are greater, hence, recovery is faster. Furthermore, anodal recovery is faster than cathodal recovery in all three cats. The effects of stimulus level are similar with biphasic stimuli and in two animals biphasic pulse trains showed faster recovery for cathodal-first pulses.

Comparison of the second-pulse responses and steady-state responses described above suggest that a cumulative adaptation effect can occur in the auditory nerve with pulse train stimulation. In order to further assess the degree of these cumulative adaptation effects, we made comparisons of the normalized responses to the second pulse, third pulse, and the steady-state response at specific IPIs for each species. Figure 13 and Figure 14 summarize the data from cats and guinea pigs, respectively, by plotting response to the second pulse, the third pulse, and the steady-state responses obtained at two stimulus levels and two polarities. In these plots, responses were collected using an IPI of 1 ms. This IPI was chosen because amplitude

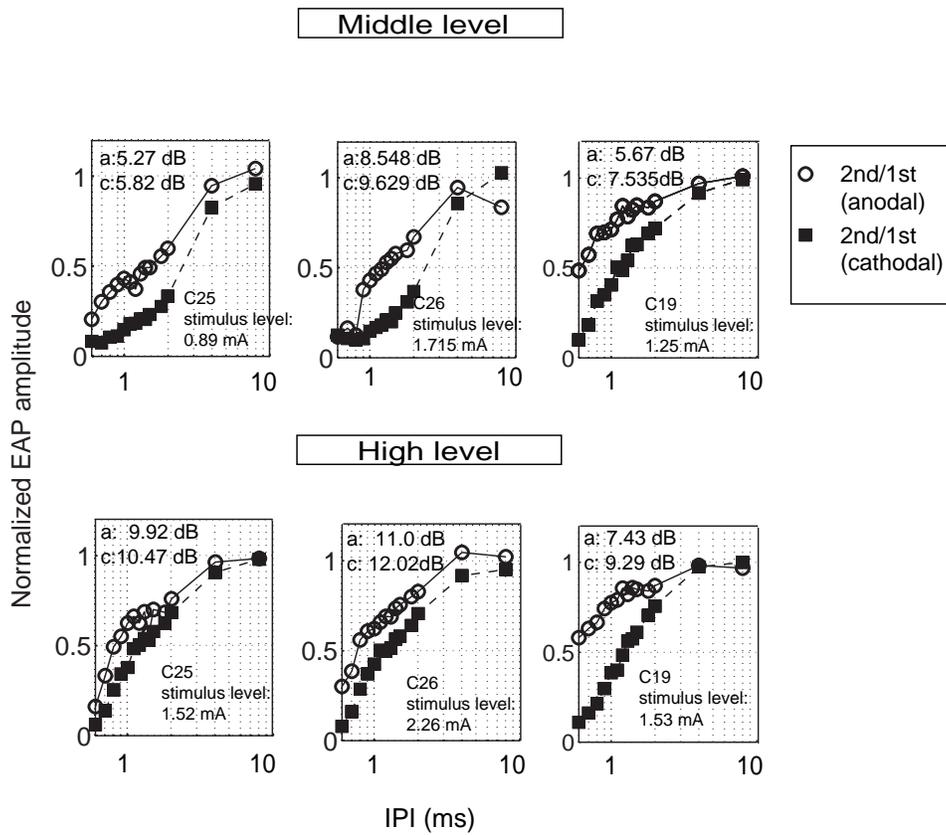


Figure 11: Normalized EAP response amplitudes plotted as a function of IPI for three cats stimulated with pseudomonophasic pulse trains. The stimulus levels used were middle and high level, which are listed in dB re threshold on each plot for both anodal and cathodal stimulation.

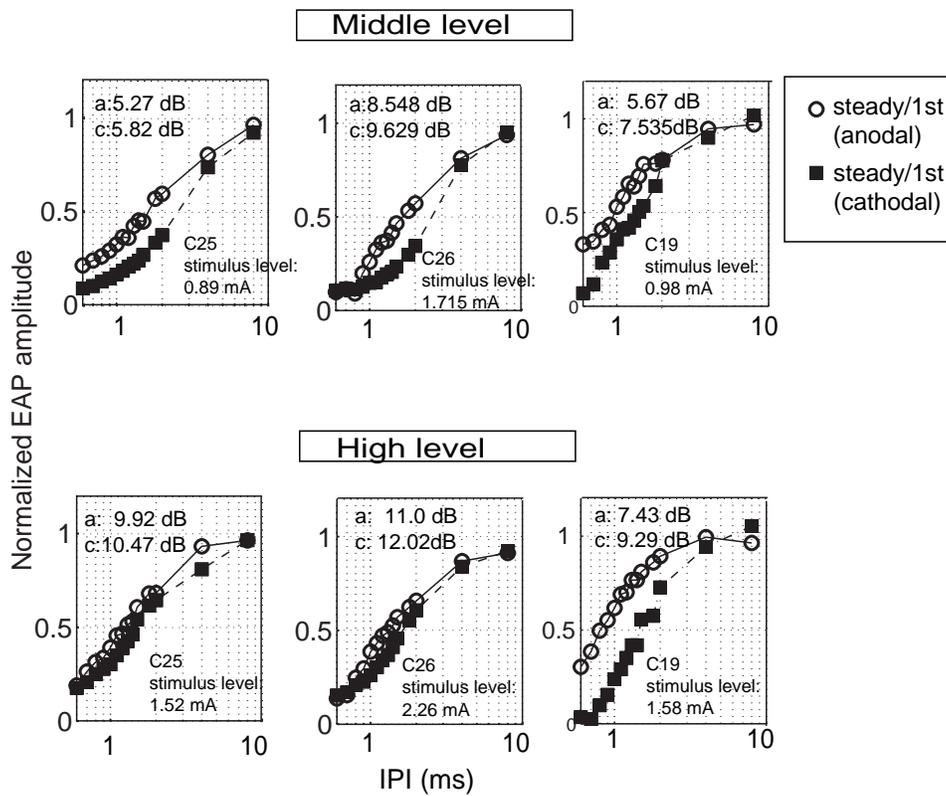


Figure 12: Normalized steady-state EAP amplitudes vs. IPI for three cats stimulated with pseudomonophasic pulse trains. The stimulus levels used for this were middle and high level, which are listed in dB re threshold in each plot for both anodal and cathodal stimulation.

differences between the response to the second pulse and the steady-state response tended to be greatest at that interval. In each case, t-tests were used to test statistical differences among each response measures (second vs. third vs. steady state) and are indicated in each figure. Anodal stimuli generally yielded amplitude decrements across these three response measures, suggesting relatively greater adaptation over the duration of the pulse train. While there is some indication of this trend in both species, it is not as consistent in guinea pig. Similar analyses with biphasic pulse trains (not shown) demonstrated a similar, though less consistent, trend.

### 3.5 Effect of IPI on response alternation

We also examined the relationship between EAP alternation pattern and IPI. Maximum alternation amplitude is plotted as a function of IPI in Figures 15 and 16. For anodal stimuli, the maximum alternation occurs at short IPIs (less than 1 ms) at both stimulus levels. In all three cats and in two guinea pigs, medium level cathodal stimuli demonstrate a peak at a relatively long IPI (approximately 2 ms) and show a peak similar to anodal stimuli at high levels. The differences with polarity are likely related to different refractory characteristics. These trends are readily apparent in the pseudomonophasic data, but are not so robust in the biphasic data.

The EAP amplitude characteristics in response to pulse trains for guinea pigs were similar in many respects to those of the cat. Effects of stimulus level were similar in that both showed an increase in alternation with increasing level. Maximum alternation generally occurred at a level near EAP amplitude saturation. Both species showed maximum alternation at different IPIs for anodal and cathodal stimuli. The effect of stimulus polarity was less consistent in guinea pig than in cats. Both species showed clear level effects in the recovery. Cats showed clear differences in recovery with IPI for different polarity stimuli, which was not evident in the guinea pig data. Finally, while alternation varied with many stimulus parameters, the degree of alternation tended to be greater in guinea pigs than in cats. Figure 17 summarizes the alternation amplitude in both species. A t-test shows significant difference between cat and guinea pig ( $p < 0.0000001$ ).

### 3.6 Response characteristics in noise

Since guinea pigs generally showed a greater degree of response alternation than cats, they were used in subsequent studies investigating the effects of

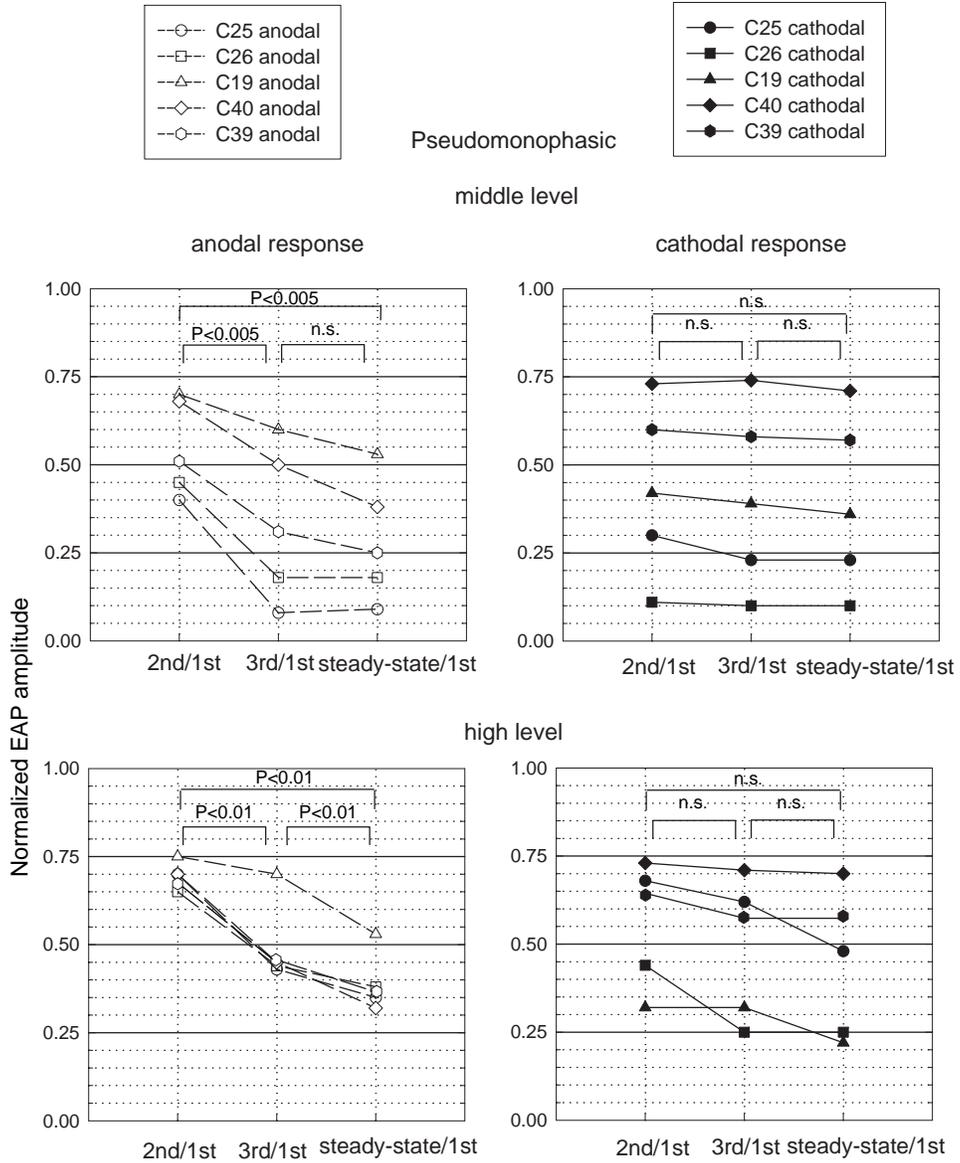


Figure 13: Normalized EAP response amplitude to the second pulse, third pulse, and steady-state responses plotted for five cats. Data are plotted for two levels (middle and high) and for anodal and cathodal pulses. All data were collected with pseudomonophasic pulse trains at an IPI of 1 ms. Paired t-test are performed for the comparison among the conditions and results are shown in each plot.

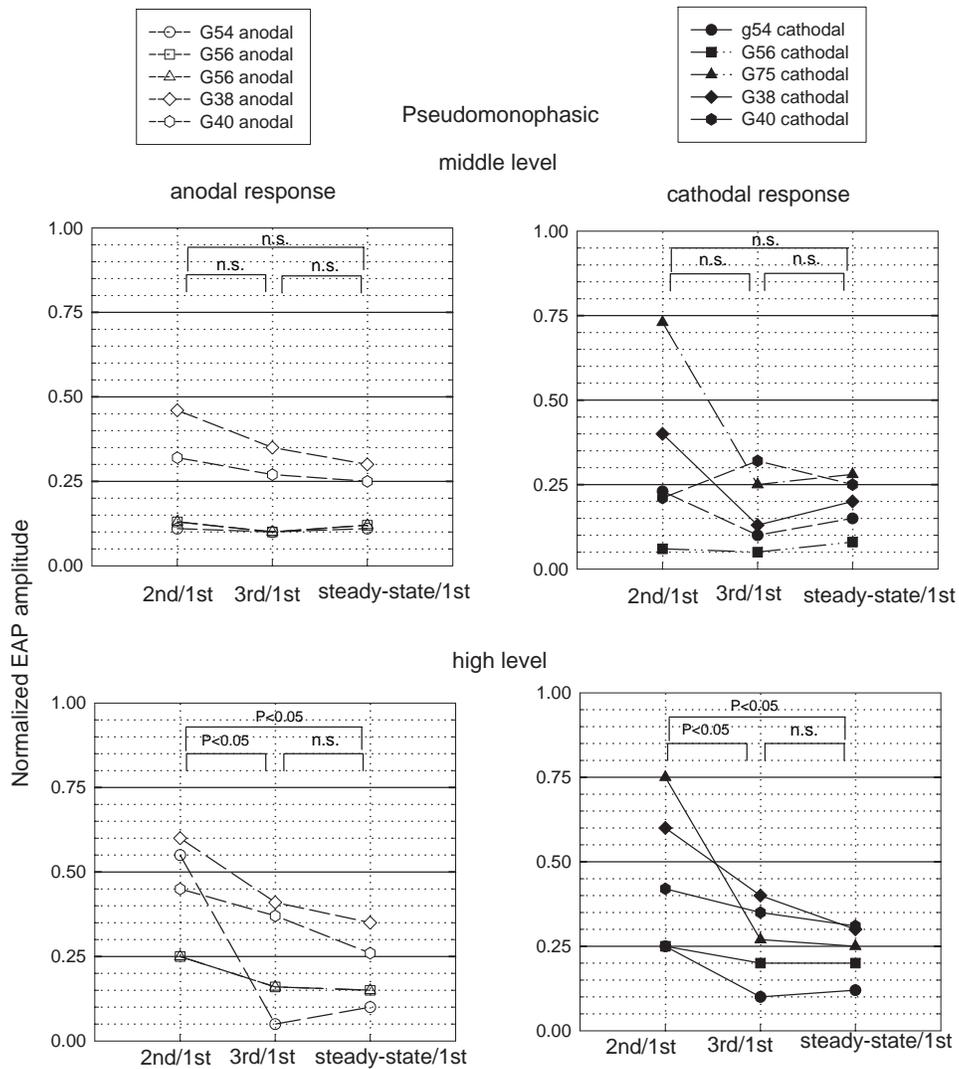


Figure 14: Normalized EAP response amplitude to the second pulse, third pulse, and steady-state responses are plotted for five guinea pigs. Data are plotted for two levels (middle and high) and for anodal and cathodal pulses. All data were collected with pseudomonophasic pulse trains at an IPI of 1 ms. Paired t-test are performed for the comparison among the conditions and results are shown in each plot.

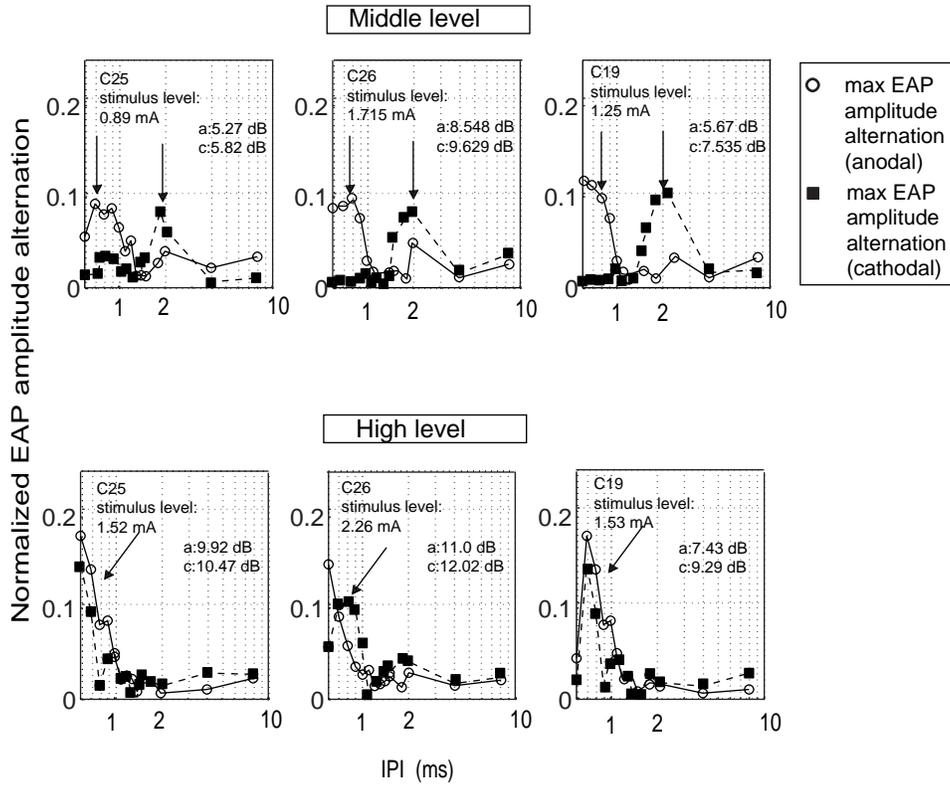


Figure 15: Maximum alternation amplitude is plotted as a function of IPI for three cats stimulated with pseudomonophasic pulse trains. In each graph, data for anodal and cathodal stimuli are plotted. Graphs represent data for two stimulation levels (middle and high) and three subjects (C25, C26, and C19).

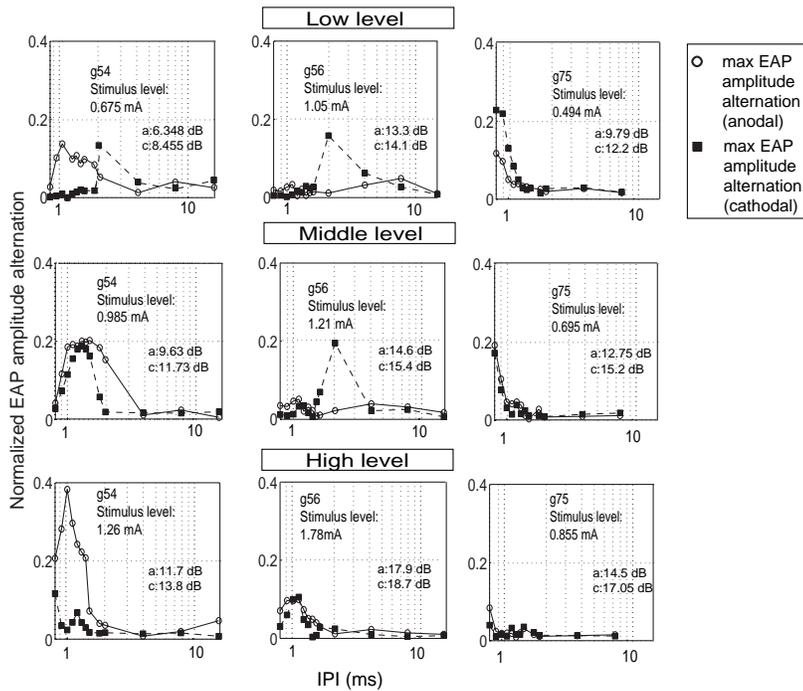


Figure 16: Maximum alternation amplitude is plotted as a function of IPI for three guinea pigs (pseudomonophasic pulse trains). In each graph data for anodal and cathodal stimuli are plotted. Graphs represent data for three stimulation levels (low, middle, and high) and three subjects (G54, G56, and G75).

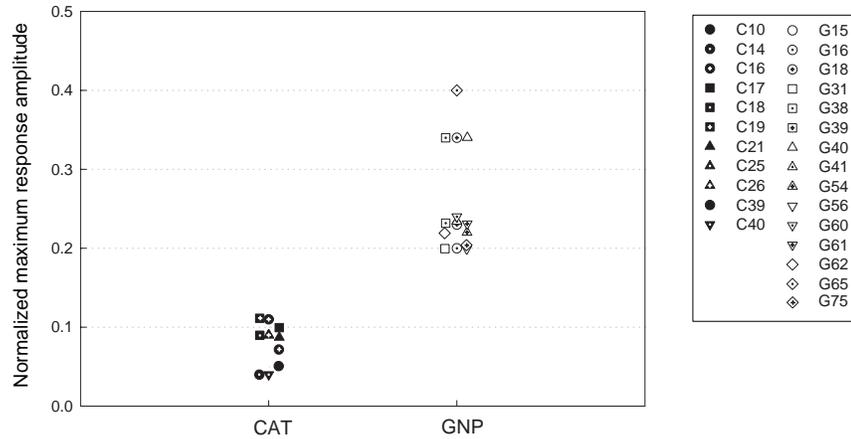


Figure 17: Comparison of maximum alternation amplitude between cats and guinea pigs. Maximum alternation amplitudes for cathodal stimuli at middle stimulus level are plotted. IPI was varied from 0.6 ms to 8 ms and a maximum value was chosen for each animal. Stimulus was biphasic pulse train for C10, C14, C16, C17, G15, G16, G18, G31, G38, and G40. All others were pseudomonophasic pulse trains.

noise and high rate pulses in decreasing the degree of alternation. Figure 18 shows EAP response patterns to pseudomonophasic pulse trains at the IPI (0.8 ms) at which maximum alternation was observed. The level of continuous noise added to the pulse train stimuli is indicated in each plot. The stimulus level for the pulse train is 1.63 mA, at the level which the EAP growth function reached saturation. Without noise (level of 0  $\mu$ A), an alternating pattern of response amplitude was evident. A similar pattern was seen for noise levels up to 3.5  $\mu$ A. The degree of alternation decreased at noise levels of 6.8 and 8.8  $\mu$ A. Above 9.8  $\mu$ A, there was an increased variation in the response amplitude, but the pattern was irregular rather than alternating. When the noise was turned off, the same alternating pattern was again observed, demonstrating that the effect is reversible. These data suggest that at certain noise levels, we can create a desynchronization across stimulus presentations resulting in smaller averaged responses, but with a more uniform response amplitude across the pulse train.

To assess the effectiveness of the additive noise, measures of maximum alternation amplitude were again examined. To compare the noise level at which minimum alternation was observed across animals, Figure 19 plots

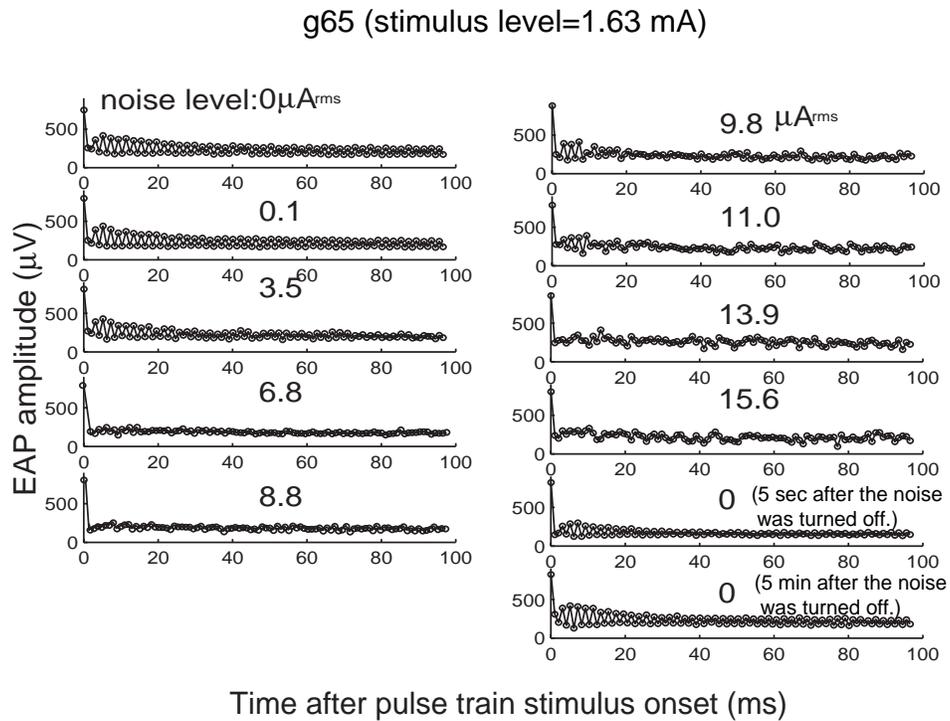


Figure 18: An example for EAP amplitude to pulse train (IPI=0.8 ms) with additive Gaussian noise (G65). The stimulus level for the pulse train was 1.63 mA, the level at which the EAP growth function reached saturation. At the end of this sequence of recordings (bottom right column) are two recordings made with no additive noise present. The upper of these two graphs is the response obtained 5 seconds after tuning off the noise stimulus. The lower graph is the response pattern recorded 5 minutes after turning off the noise stimulus.

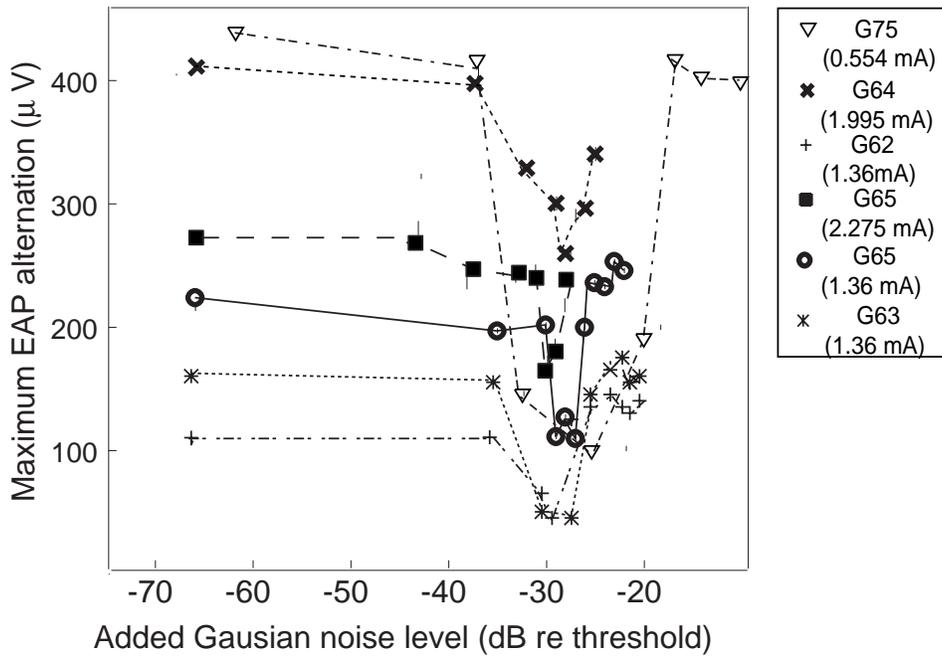


Figure 19: Response alternation amplitude as a function of additive Gaussian noise level in dB relative to EAP threshold for four subjects. Subject number and current level for the pulse train are shown in the legend.

maximum response alternation amplitude as a function of noise level referenced to EAP threshold level for each subject. Note that, in all cases, amplitude alternations decrease for noise levels near -30 dB. This result suggests that the of noise level, expressed relative to threshold, may be a meaningful index for determining its optimal, most effective, level.

### 3.7 Response to low and high-rate pulse trains

Before examining an effect of combining a high-rate conditioning pulse train with a low-rate pulse train, we measured the EAP responses to low-rate and high-rate pulse trains presented separately. Figure 20 shows the EAP amplitude in response to a low-rate pulse train as well as in response to high-rate pulse train (which is used as conditioner stimulus in subsequent the experiments). In each case, the EAP amplitude to each pulse is plotted

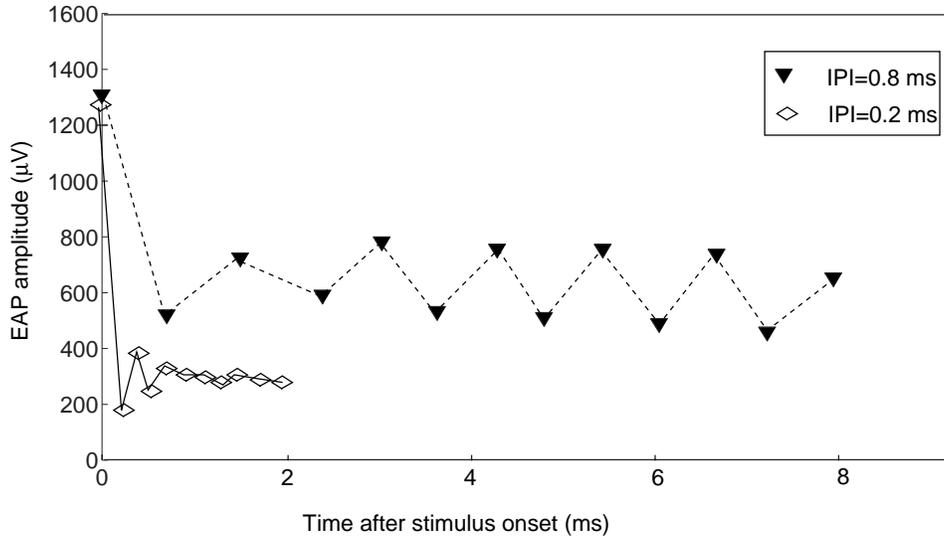


Figure 20: EAP response amplitudes as a function of time after stimulus onset for two different IPIs (IPI = 0.2 ms and 0.8 ms). Stimulus level used is 0.72 mA.

versus time after stimulus onset. The alternating pattern of response amplitude is evident with an IPI of 0.8 ms. Using the same stimulus level with an IPI of 0.2 ms, the response amplitude is constant after the first few stimulus pulses. Note that response amplitudes are smaller than those with an IPI of 0.8 ms, suggesting that a smaller number of fibers were responding to each pulse in the high-rate trains. The data are quite similar to data from humans reported by Wilson et al. ( ). Such examples are consistent with a model that a high-rate conditioner may create random spike pattern in auditory nerve fibers which may reduce the alternating pattern in the EAP response amplitude (Rubinstein et al., 1998).

Figure 21 is an example of the EAP response to a low-rate stimulus (IPI = 0.8 ms) with different levels of high-rate pulse train conditioners (IPI=0.2 ms) interleaved. Note that high-rate stimulation precedes the onset of low-rate stimulation by 50 ms (see Figure 3). Also note that, in these cases, because it is necessary to use a time-consuming subtraction method, responses are only characterized over the first 8 ms of the pulse train. In these experiments, the low rate stimulus is equivalent to the pulse trains measured in previous sections in that the response to each pulse is measured.

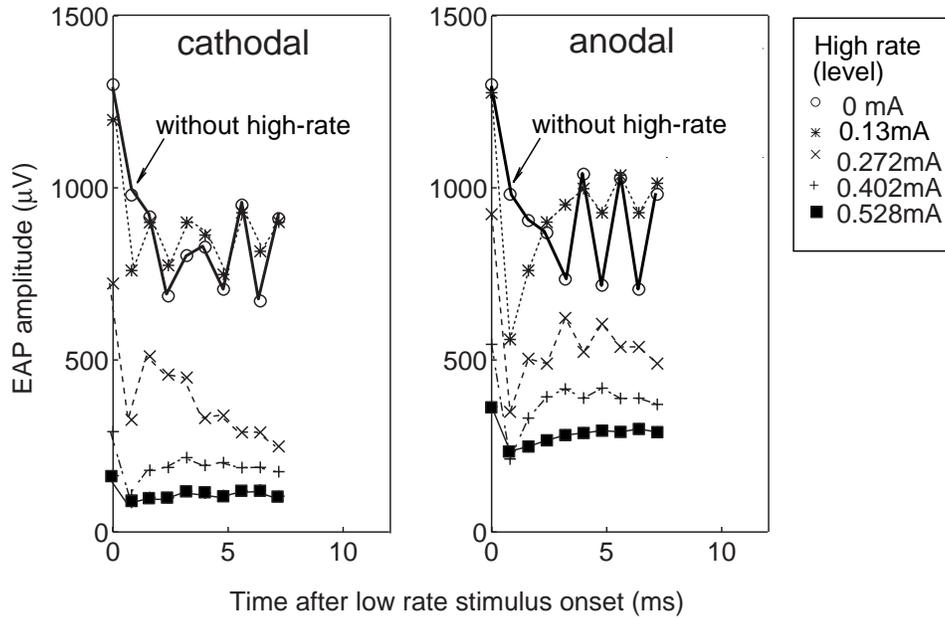


Figure 21: An example of responses to low-rate pulse train (0.76 mA with IPI =0.8 ms) with different high-rate conditioners (IPI=0.2 ms). Anodal and cathodal responses are shown. Level of the high-rate conditioner is shown in the graph.

Each of the plots shows response to the individual low-rate pulse in the train for different levels of the high-rate conditioner. As the level of the high-rate stimulus increases, both the degree of alternation and average response to low-rate stimuli decreases. The decrement in the alternation pattern suggests that the high-rate pulse train stimulation may desynchronize the nerve's response to the low-rate pulse train. Also note that as the high-rate stimulus level is increased, the response to the second pulse decreases, suggesting the response to the second pulse is in a more refractory state.

Figure 22 summarizes the data from four animals, showing maximum alternation amplitude of low-rate pulse trains (left side) as well as steady-state response amplitude of low-rate pulse train (right side) as a function of high-rate conditioner level. The maximum alternation amplitude is defined in the same manner as in the previous section. The steady-state response amplitude is defined as the average of response to the last five pulses in the train, because there are only ten pulses to calculate the steady-state

response for this experiment. The group in the first row shows data similar to the first example (see Figure 21). In addition to these examples, two other patterns of response alternation with level were observed. We refer to these different patterns as types A, B, and C response patterns. In type A response pattern, the degree of maximum alternation monotonically decreases with a high rate conditioner level. Steady-state response is also monotonically decreasing. Type B responses show similar trends, but at high levels an increase in alternation is observed. Similar to type A, steady-state response monotonically also decreases with high-rate conditioner level. For type C responses, we observed little or no alternation without the high-rate conditioner. Increasing the high-rate level increases alternation except at high levels where there is a decrease in alternation. There was little effect on steady-state responses in these animals.

### 3.8 Summary and discussion

In this report, the characteristics of the EAP in response to constant-amplitude electrical pulse trains were described for guinea pig and cat preparations, as well as a stochastic axonal model. Several trends were observed in the data. A characteristic pattern of alternating response amplitudes, presumably due to refractory effects, was found dependent on several stimulus parameters. The amplitude of the response alternation was a nonmonotonic function of stimulus level, showing a maximum near the level necessary to reach the maximum in the EAP amplitude- level (i.e., growth) function. Response alternation was also highly dependent on interpulse interval. This dependence was different for anodic and cathodic stimulus polarities. The degree of response alternation was found to be consistently greater in guinea pigs than in cats. Also, effects observed by changing stimulus polarity were relatively more robust in the cat preparations. We suggest that these interspecies differences may result from anatomical differences between the cochleae of the two species, which may, in turn, give rise to different modes of neural excitation, as has been previously suggested (Miller et al., 1998). In future work, it may be propitious to better understand the factors underlying these interspecies differences.

The degree of response decrement, measured relative to the response to the first pulse, was used to assess EAP recovery from refractory effects. Recovery was level-dependent, with higher stimulus levels resulting in faster recovery. It was also polarity dependent, with anodal stimuli having faster recovery. In addition, with anodal stimuli, the steady-state ampli-

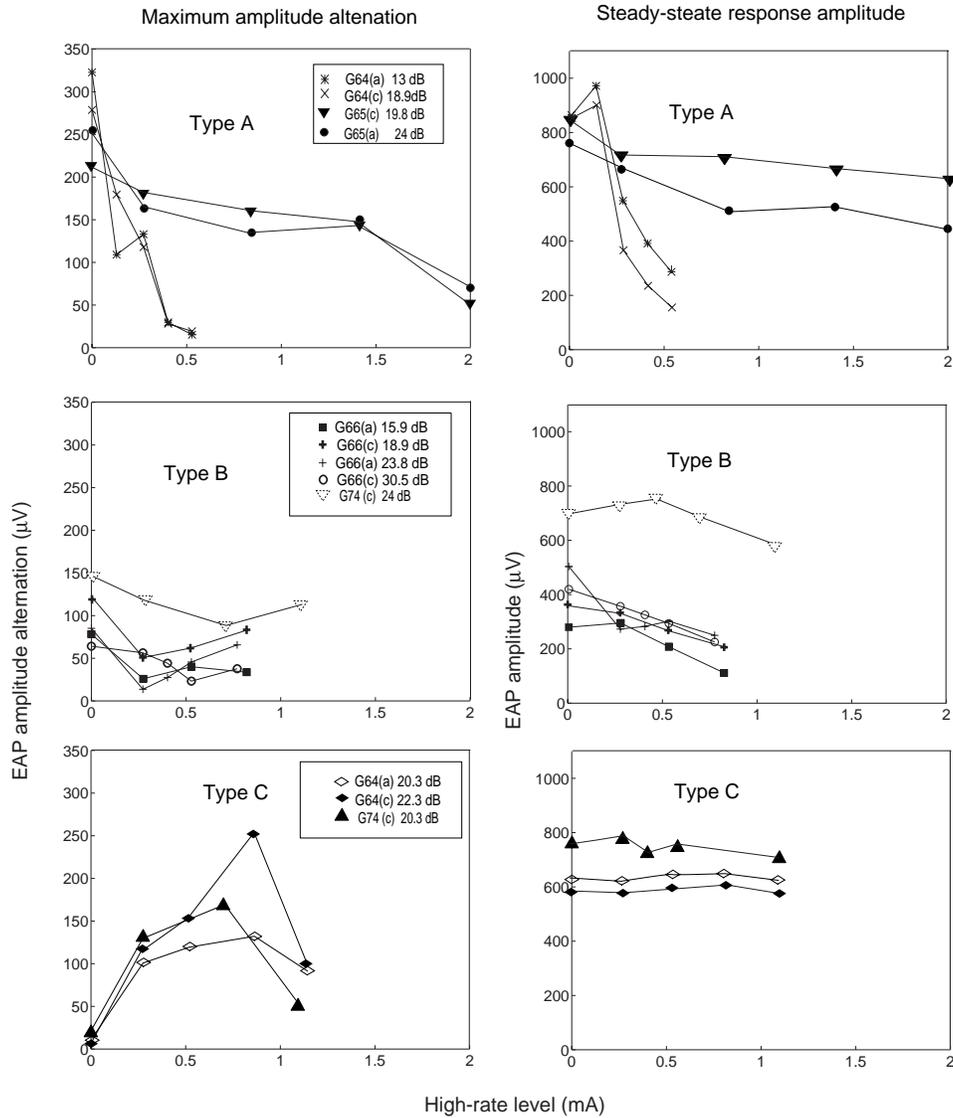


Figure 22: Plots of maximum alternation amplitude of low-rate pulse trains (left column) and steady-state response amplitude of low-rate pulse trains (right column) as a function of high-rate conditioner level. Examples are shown for three different response alternating pattern observed in this study (type A, B, and C). Subject number, polarity and stimulus levels for low-rate pulse trains indicated as dB re threshold are shown in the legend.

tude showed a greater decrease than that observed with the second or third pulse in the train, suggesting a cumulative effect with that stimulus polarity. We noted that stimulus-polarity effects were more evident with the use of pseudomonophasic stimuli than with biphasic stimuli, suggesting that pseudomonophasic waveforms may possess unique utility in assaying response properties of the auditory nerve.

The degree of response alternation was found to be affected by the addition of either of two conditioning stimuli: noise or high-rate pulse trains. In both cases, the decrease in alternation was highly dependent on the level of the conditioning stimulus relative to the subject's EAP threshold. Such stimulus paradigms may have practical application to new implementations of implant speech processors. The simultaneous use of such conditioning stimuli with other types of stimuli, such as amplitude-modulated pulse trains, will be the subject of further study.

General patterns of the responses recorded here are similar to those recorded in human cochlear implant users (Wilson et al., 1994). However, potentially important details described in our animal experiments, such as the degree of response alternation and the effects of stimulus level, are not in complete agreement. Thus, in order to apply the results presented here as a model of human implant users, it is essential to gain a better understanding of the differences between humans and experimental animals. The present data comparing cats and guinea pigs provides some important insights into these differences. For instance, as noted above, the effects stimulus polarity appear, in all of our data, to be more consistent in cat than in guinea pig. Across-species anatomical differences may, therefore, be relevant. Also, the physiological status of the auditory nerve in our animal preparations is, presumably, more normal than in the typical implanted human ear. Future experiments planned in the third year of this contract will investigate responses in guinea pigs with varying degrees of degeneration of the auditory nerve and possibly help explain some of the observed differences. Analysis of data from animals with degenerated spiral ganglion cells may also suggest specific experiments to conduct with human implant users in the future.

## **4 Plans for the next quarter**

- Complete single-fiber and EAP data analysis of the last cat experiment (C41) conducted in the 7th quarter.
- Complete preparation of a manuscript relating single-fiber responses

to the gross, whole-nerve, response. Submit this and a companion paper to a journal for consideration for publication.

- Modify model parameters to better simulate single fiber measures reported in QPR 6.
- Run model simulations of responses to amplitude modulated pulse trains. If appropriate, use those results to suggest further physiological experiments and incorporate model results into manuscript describing results with amplitude modulation.
- Prepare presentations for the 1st International Symposium and Workshop on Objective Measures in Cochlear Implantation, to be held in Nottingham, England.
- Complete deafening of guinea pigs to be used in the last phase of this contract dealing with chronically deafened preparations.

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## **A Presentations given during this reporting period**

Rubinstein, J.T. (1998). New directions in signal processing. 7th Symposium on Cochlear Implants in Children, Iowa City, IA.

Miller, C.A., Abbas, P.J., Rubinstein, J.T., Matsuoka, A.J. and Robinson, B.K. (1998). Ongoing research at the University of Iowa Electrophysiology Lab: Efforts to improve implant performance. 7th Symposium on Cochlear Implants in Children, Iowa City, IA.

Rubinstein, J.T., Wilson, B.S, and Abbas, P.J. (1998). Restoration of acoustic-like patterns of auditory nerve activity with electrical stimulation. Fourth European Symposium on Pediatric Cochlear Implantation, s'-Hertogenbosch, The Netherlands.